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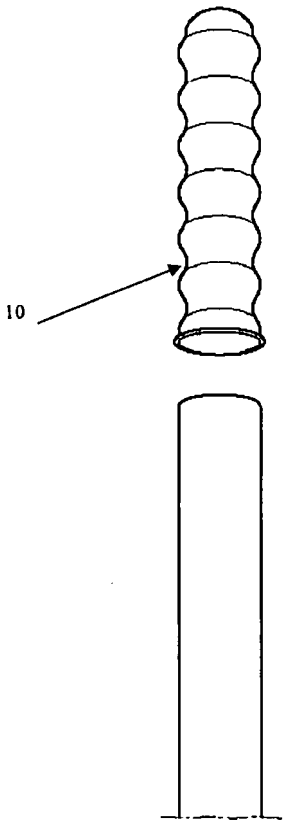
(54) Title: DEVICE FOR TREATMENT OF RECTAL DISORDERS, AND MANUFACTURING PROCESS FOR THE SAME, INVOLVING NITRIC OXIDE



(57) Abstract: A device for therapeutic treatment of rectal disorders, including fissures, ulcers, haemorrhoids, and levator spasm, is disclosed. The device comprises a nitric oxide (NO) eluting polymer configured for eluting a therapeutic dosage of nitrogen oxide (NO) when used for the treatment. Furthermore, the device is configured for exposing a rectal treatment site of said rectal disorder in or on a rectal region of a body to said nitric oxide when said polymer elutes nitrogen oxide (NO). The nitric oxide (NO) eluting polymer is integrated with a carrier material, such that said carrier material, in use, regulates and controls the elution of said therapeutic dosage of nitric oxide (NO). Moreover a method of manufacturing such a rectal treatment device is disclosed.

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DEVICE FOR TREATMENT OF RECTAL DISORDERS, AND MANUFACTURING PROCESS FOR THE SAME, INVOLVING NITRIC OXIDE

Field of the Invention

This invention pertains in general to the field of treatment of rectal disorders, and in particular fissures, ulcers, haemorrhoids or levator spasm. More particularly the invention relates to a device for the therapeutic treatment of rectal disorders, and in particular fissures, ulcers, haemorrhoids or levator spasm, and a process for manufacturing of said device, involving the use of nitric oxide (NO).

Background of the Invention

Rectal disorders, such as fissures, ulcers, haemorrhoids and levator spasm, are very common among adults in the world. Calculations estimate that over 50 percent of the population sometime experience these kinds of disorders. These disorders are often caused by the hectic way of life in the world of today, such as stress, straining, bad diet, and standing during long periods of time, or for instance after impacts on the rectal region when giving birth to a child.

Rectal fissures are small tears or cuts in the skin lining the anus. The symptoms of rectal fissures are blood in stool and pain during defecation. Rectal fissures may be acute, usually due to altered bowel habits, and chronic, deriving from bad bowel habits or an underlying medical problem. Today, the only treatment consists of keeping good hygiene, eating a healthy diet, and sometimes surgery.

Rectal ulcers may develop from many medical problems, such as ulcerative colitis, cancer, Crohn's disease, herpes, HIV etc. The common practice for treatment of rectal ulcers developed from medical problems, according to the background of the invention, is surgery. Needless to say, surgery is a method of treatment that causes great discomfort to the patient, and surgery is always a

complicated procedure. In some cases medications are used, such as the hydrocortisone Proctofoam. These treatments are based on cortisone treatment. It is well documented that cortisone treatment does cause drug resistance against the cortisone. Moreover, the over exposure to cortisone has other adverse side effects on the human body.

Haemorrhoids are enlarged veins, just under the surface tissue, of rectum. Haemorrhoids that occur in rectum are called internal haemorrhoids, and those that occur around anus are called external haemorrhoids. The cause of haemorrhoids is not well documented, but causative suggestions are stress, straining, bad diet, and standing during long periods of time. Pregnant women often suffer from haemorrhoids. Up to this point haemorrhoids are treated with different kinds of creams, suppositories, ointments, containing different active substances, such as cortisone. These treatments are mainly based on cortisone treatment. Advanced treatments include sclerotherapy, which is an injection of a substance that shrinks the blood vessels, banding, which is an application of a tight elastic band around the haemorrhoid to cut of its blood supply, or surgical operation. These treatments are painful procedures. Moreover, these are treatments that need the assistance of a physician, and are therefore incompatible with self-treatment.

Levator spasm, or levator ani, is a functional anal disorder associated with great pain. The cause of the pain is a spasm in the muscles in the pelvic floor. This condition is very difficult to treat. The treatments according to the background of the invention include high voltage electro galvanic stimulation of the levator ani muscle, massage of the levator ani muscle, or medications, such as ibuprofen or naproxen. Treatment with high voltage electro galvanic stimulation is, needless to say, extremely painful, and requires equipment that the person suffering

from levator spasm cannot keep at home. Therefore, this kind of treatment cannot give the patient an immediate relief of pain. Massage and medications do only offers moderate and momentary pain relief, and are not treatments giving a long lasting treatment of levator spasm.

It is known that nitric oxide (NO) provides an alternative to conventional therapies, such as antibiotics. Nitric oxide is a highly reactive molecule that is involved in many cell functions. In fact, nitric oxide plays a crucial role in the immune system and is utilized as an effector molecule by macrophages to protect itself against a number of pathogens, such as fungi, viruses, bacteria etc., and general microbial invasion. This improvement of healing is partly caused by NO inhibiting the activation or aggregation of blood platelets, and also by NO causing a reduction of inflammatory processes at the site of an implant.

NO is also known to have an anti-pathogenic, especially an anti-viral, effect, and furthermore NO has an anti-cancerous effect, as it is cytotoxic and cytostatic in therapeutic concentrations, i.e. it has among other effects tumoricidal and bacteriocidal effects. NO has for instance cytotoxic effects on human haematological malignant cells from patients with leukaemia or lymphoma, whereby NO may be used as a chemotherapeutic agent for treating such haematological disorders, even when the cells have become resistant to conventional anti-cancer drugs. This anti-pathogenic and anti-tumour effect of NO is taken advantage of by the present invention, without having adverse effects as for instance many anti-cancer drugs.

However, due to the short half-life of NO, it has hitherto been very hard to treat viral, bacteria, virus, fungi or yeast infections with NO. This is because NO is actually toxic in high concentrations and has negative effects when applied in too large amounts to the body. NO

is actually also a vasodilator, and too large amounts of NO introduced into the body will cause a complete collapse of the circulatory system. On the other hand, NO has a very short half-life of fractions of a second up to a few seconds, once it is released. Hence, administration limitations due to short half-life and toxicity of NO have been limiting factors in the use of NO in the field of anti-pathogenic and anti-cancerous treatment so far.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least one $-NO_X$ group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythiolated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of medical devices to be permanently implanted in the body, such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such devices. According to US-6,737,447, a coating for medical devices provides nitric oxide delivery using nanofibers of linear poly(ethylenimine)-diazeniumdiolate. Linear poly(ethylenimine)diazeniumdiolate releases nitric oxide (NO) in a controlled manner to tissues and organs to aid the healing process and to prevent injury to tissues at risk of injury.

However, the meaning of "controlled" in the context of US 6,737,447 is only directed to the fact that nitric

oxide is eluted from the coating during a period of time. Therefore, the interpretation of "controlled" in respect of US 6,737,447 is different from the meaning of "regulating" in the present invention. "Regulate", according to the present invention is intended to be interpreted as the possibility to vary the elution of nitric oxide to thereby achieve different elution profiles.

Electrospun nano-fibers of linear poly(ethylenimine) diazeniumdiolate deliver therapeutic levels of NO to the tissues surrounding a medical device while minimizing the alteration of the properties of the device. A nanofiber coating, because of the small size and large surface area per unit mass of the nanofibers, provides a much larger surface area per unit mass while minimizing changes in other properties of the device.

WO 99/16436 discloses oral and rectal administration of nitric oxide to a patient for treating inflammatory bowel disease. Such inflammatory diseases may for example be ulcerative colitis. The nitric oxide is carried in a nitric oxide donor, such as examples of S-nitrosylated compounds, which is not a polymer. Furthermore, nothing is mentioned in WO 99/16436 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating gastric ulcers and haemorrhoids.

US 6,737,447 discloses a coating for medical devices, which coating provides NO delivery by using nanofibers of L-PEI. The medical devices according to US 6,737,447 are exemplified as catheters, stents, vascular grafts, wound dressings, and the like. Furthermore, nothing is mentioned in US 6,737,447 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating levator spasm or haemorrhoids.

US 5,770,645 discloses polymers with Nox-groups, such as S-nitrosylated polymers. These polymers can be used to coat medical devices to deliver nitric oxide in vivo to

treatment sites. Examples of medical devices according to US 5,770,645 is in-dwelling sheaths (venous and arterial), intraaortic balloon pump catheters, tubes in heart lung machines, GORE-TEX surgical prosthetic conduits, in-dwelling urethral catheters, PTCA-balloon catheters, stents, etc. Non-vascular treatment-sites are also mentioned in, such as gastrointestinal and bladder disorders. Thus, nothing is mentioned in US 5,770,645 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating levator spasm or haemorrhoids.

EP 1 300 424 discloses extremely hydrophobic NO releasing polymers. These polymers are extensively cross-linked polyamine-derivatized divinylbenzene diazeniumdiolates. The treatments mentioned in EP 1 300 424 are angiogenesis, restenosis, reduce thrombogenicity, and wound healing. Since the polymer according to EP 1 300 424 is extremely hydrophobic, and highly resistant to penetration by water and insoluble therein, the elution of nitric oxide has to be initiated by something else than water. Thus, nothing is mentioned in EP 1 300 424 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating levator spasm or haemorrhoids.

US 2004/0171589 discloses local, differential delivery of nitric oxide within the body. D5 discloses polyethyleneimine microspheres, with an attached diazeniumdiolate moiety, for long in-situ half-life applications. The medical devices are vascular medical devices, urological medical devices, biliary medical devices, gastrointestinal medical devices, medical devices adapted for placement on surgical sites, and medical devices adapted for placement on skin wounds or openings. Thus, nothing is mentioned in US 2004/0171589 about regulating or controlling the elution of nitric oxide, and

nothing is mentioned about treating levator spasm or haemorrhoids.

US 2002/0022046 discloses methods to inhibit or prevent restenosis or improve vascular function. Nitric oxide is eluted from a polyurea network. Thus, nothing is mentioned in US 2002/0022046 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating levator spasm or haemorrhoids.

WO 01/26702 discloses site-specific delivery of nitric oxide by entrapping nitric oxide releasing polyethyleneimine microspheres in the pores of a vascular graft. Thus, nothing is mentioned in WO 01/26702 about regulating or controlling the elution of nitric oxide, and nothing is mentioned about treating levator spasm or haemorrhoids.

However, the disclosure is both silent concerning an improvement of present technology in respect of treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm, and the anti pathogenic potential of nitric oxide, and also concerning regulating the elution of nitric oxide.Hence, an improved device, or more advantageous, for the treatment and/or prevention of rectal disorders, is needed in the art. It is desired that said device does not develop resistance against the active pharmaceutical substance, is easy to apply, provides a painless treatment, has fast inset of treatment effect, and exclude the necessity of surgery, would be advantageous, and in particular a device allowing for target prevention and treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm, would be advantageous.

Summary of the Invention

Accordingly, the present invention preferably seeks to mitigate, alleviate or eliminate one or more of the

above-identified deficiencies in the art and disadvantages singly or in any combination and solves, among others, at least some of the problems mentioned above, by providing a device and manufacturing method according to the appended patent claims.

According to one aspect of the invention, a device is provided that allows for target treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm. The device comprises a nitric oxide (NO) eluting polymer arranged to contact the area to be treated, such that a therapeutic dose of nitric oxide is eluted from said nitric oxide eluting polymer to said area.

According to another aspect of the invention, a manufacturing process for such a device is provided, wherein the process is a process for forming a device that allows for target treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm. The process comprises selecting a plurality of nitric oxide eluting polymeric particles, such as nano fibres, fibres, nano particles, or microspeheres, and deploying said nitric oxide eluting particles in a condom/sheath or tape/coating to be comprised in said device.

The present invention has at least the advantage over the prior art that it does not develop resistance against the active pharmaceutical substance, is easy to apply, provides a painless treatment, has fast inset of treatment effect, and exclude the necessity of surgery target, by the exposure of an infected area to NO, whereby a very effective anti-fissure, anti-ulcer, anti-haemorrhoid and/or anti-levator spasm therapy is achievable.

According to still another aspect of the present invention, a use of nitric oxide in a medicament to treat or prevent levator spasm, fissures, ulcers, and haemorrhoids is provided.

Brief Description of the Drawings

These and other aspects, features and advantages of which the invention is capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

Fig. 1 is a schematic illustration of a condom/sheath according to an embodiment of the invention,

Fig. 2 is a schematic illustration of a condom shaped patch 20 according to an embodiment of the invention,

Fig. 3 is a schematic illustration of a tampon 30 according to an embodiment of the device of the invention,

Fig. 4 is a schematic illustration of a rod 40 comprised in an embodiment of the invention, and

Fig. 5 is an illustration of two elution profiles (NO concentration vs. time) for two different polymer mixtures.

Description of Embodiments

The following description focuses on embodiments of the present invention applicable to a device, for instance in form of a condom/sheath or tampon-like device, which allows for target treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm.

With regard to nitric oxide (nitrogen monoxide, NO), its physiological and pharmacological roles have attracted much attention and thus have been studied. NO is synthesized from arginine as the substrate by nitric oxide synthase (NOS). NOS is classified into a constitutive enzyme, cNOS, which is present even in the normal state of a living body and an inducible enzyme, iNOS, which is produced in a large amount in response to a certain stimulus. It is known that, as compared with the concentration of NO produced by cNOS, the concentration of

NO produced by iNOS is 2 to 3 orders higher, and that iNOS produces an extremely large amount of NO.

In the case of the generation of a large amount of NO as in the case of the production by iNOS, it is known that NO reacts with active oxygen to attack exogenous microorganisms and cancer cells, but also to cause inflammation and tissue injury. On the other hand, in the case of the generation of a small amount of NO as in the case of the production by cNOS, it is considered that NO takes charge of various protective actions for a living body through cyclic GMP (cGMP), such as vasodilator action, improvement of the blood circulation, antiplatelet-aggregating action, antibacterial action, anticancer action, acceleration of the absorption at the digestive tract, renal function regulation, neurotransmitting action, erection (reproduction), learning, appetite, and the like. Heretofore, inhibitors of the enzymatic activity of NOS have been examined for the purpose of preventing inflammation and tissue injury, which are considered to be attributable to NO generated in a large amount in a living body. However, the promotion of the enzymatic activity (or expressed amount) of NOS (in particular, cNOS) has not been examined for the purpose of exhibiting various protective actions for a living body by promoting the enzymatic activity of NOS and producing NO appropriately.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible. Another advantage is that NO is released without any secondary products that could lead to undesired side effects.

The polymers according to the present invention may be manufactured by electro spinning, gas stream spinning, air spinning, wet spinning, dry spinning, melt spinning, and gel spinning. Electro spinning is a process by which a suspended polymer is charged. At a characteristic voltage a fine jet of polymer releases from the surface in response to the tensile forces generated by interaction by an applied electric field with the electrical charge carried by the jet. This process produces a bundle of polymer fibres, such as nano-fibres. This jet of polymer fibres may be directed to a surface to be treated.

Furthermore, US 6,382,526, US 6,520,425, and US 6,695,992 disclose processes and apparatuses for the production of such polymeric fibres. These techniques are generally based on gas stream spinning, also known within the fiber forming industry as air spinning, of liquids and/or solutions capable of forming fibers.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least one -NOX group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythiolated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of permanently implanted medical devices such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such devices. According to US-6,737,447, a coating for medical devices provides nitric oxide delivery using nanofibers of linear poly(ethylenimine)-diazeniumdiolate. Linear poly(ethylenimine)diazeniumdiolate releases nitric oxide (NO) in a controlled manner.

However, the meaning of "controlled" in the context of US 6,737,447 is only directed to the fact that nitric oxide is eluted from the coating during a period of time, i.e that the nitric oxide not is eluted all in once. Therefore, the interpretation of "controlled" in respect of US 6,737,447 is different from the meaning of "regulating" in the present invention. "Regulate or control", according to the present invention, is intended to be interpreted as the possibility to vary the elution of nitric oxide to thereby achieve different elution profiles.

A polymer comprising an O-nitrosylated group is also a possible nitric oxide eluting polymer. Thus, in one embodiment of the present invention, the nitric oxide eluting polymer comprises diazeniumdiolate groups, S-nitrosylated and O-nitrosylated groups, or any combinations thereof.

In still another embodiment of the present invention said nitric oxide eluting polymer is a poly(alkyleneimine)diazeniumdiolate, such as L-PEI-NO (linear poly(ethyleneimine)diazeniumdiolate), where said nitric oxide eluting polymer is loaded with nitric oxide through the diazeniumdiolate groups and arranged to release nitric oxide at a treatment site.

Some other examples of a suitable nitric oxide eluting polymer are selected from the group comprising amino cellulose, amino dextrans, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose, polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

In still another embodiment of the present invention the nitric oxide eluting polymer may be a O-derivatized NONOate. This kind of polymer often needs an enzymatic reaction to release nitric oxide.

Other ways of describing polymers, which may be suitable as nitric oxide eluting polymer, is polymers comprising secondary amine groups (=N-H), such as L-PEI, or have a secondary amine (=N-H) as a pendant, such as aminocellulose.

In an embodiment of the invention, according to Fig. 1, the device is in form of a latex or rubber condom/sheath 10, said condom/sheath being covered on the outside with nano-filament of NO-eluting L-PEI.

In another embodiment of the present invention the condom/sheath is covered on the outside with nano-filament of any other suitable polymer, according to above. Such polymers are for example polyalkyleneimines, such as B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible.

This condom/sheath may be in any suitable size, such as a suitable diameter size for inserting said condom/sheath in rectum. These diameter sizes may for example vary from small, medium, and large sized condoms/sheaths, such as 0.25 to 2 cm, for example 0.50 to 1 cm, such as 0.75. This condom/sheath may also vary in length, which length may be in the interval of 1 to 20 cm, such as 5 to 15 cm, for example 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 cm.

The condom/sheath according to the present invention is applied by running said condom/sheath over a suitably sized stick, and then inserting said stick in rectum. When the stick is removed, the condom/sheath left in rectum. As soon as the condom/sheath according to the present invention gets in contact with the moisture in rectum, the condom/sheath starts to elute NO on the area to be treated.

When treatment is finished or to be interrupted, the device is easily retracted from the rectal region for that purpose.

In another embodiment of the present invention the condom/sheath according to the present invention is covered on the outside with NO-eluting nano-particles, or micro-spheres. These nano-particles, or micro-spheres, may be formed from the NO-eluting polymers according to the present invention, encapsulated in any suitable material, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.. When the nano-particles, or micro-spheres, according to this embodiment, gets in contact with the moisture in rectum on the outside of the condom/sheath, they start to elute NO on the area to be treated.

In the context of the present invention the term "encapsulating" is intended to be interpreted as fixating the nitric oxide eluting polymer in a three dimensional matrix such as a foam, a film, a nonwoven mat of nano-fibers or fibers, other materials with the capability to fixate the NO eluting polymer, or enclosing the nitric oxide eluting polymer in any suitable material.

In still another embodiment the device may be manufactured in the form of a rod shaped patch, made of NO-eluting polymer according to the present invention. This rod-shaped patch is flexible, which results in that the person to be treated, in a small extension, feels the rod shaped patch during treatment.

In yet another embodiment said rod shaped patch is manufactured of a basic material, which basic material is covered with the nano-fibres, nano-particles, and/or micro-spheres according to the invention. The basic material of this rod, according to the invention, may be polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these..

In another embodiment the device according to the invention is in form of a tampon-like shape device 30, according to Fig. 3, covered on the outside of NO-eluting nano-fibres, nano-particles, or micro-spheres according to the present invention. The basic material of this tampon-like device may be any of the NO-eluting polymers according to the invention, or polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

The tampon according to the present invention may also be manufactured of other materials, including normal tampon materials, such as cotton. In this case the NO-eluting polymer, such as L-PEI, may be spun onto said tampon. The size of said tampon may vary, but in one embodiment of the present invention the size corresponds to the smallest tampon size, such as a tampon with a diameter to 1.5 cm, for example 0.50 to 1 cm, such as 0.75 cm. The

tampon according to the invention may optionally be equipped with a retracting string, for easier retraction of the tampon from rectum.

In still another embodiment of the present invention the device is a rod 40, according to Fig. 4, manufactured of NO-eluting polymer, according to the present invention.

In another embodiment said rod is manufactured as a carrier and of a basic material, which basic material is covered with the nano-fibres, nano-particles, and/or micro-spheres of NO-eluting polymer according to the invention. The basic material of this rod, according to the invention, may be polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. The NO-eluting polymer may be integrated in, or spun together with, any of these materials.

The diameter of the rod according to the invention may vary, but in one embodiment of the present invention the diameter may be in the interval 0.25 to 1.5 cm, for example 0.50 to 1 cm, such as 0.75 cm.

The rod shaped patch, the tampon, or the rod is inserted in rectum. As soon as the rod shaped patch, the tampon, or the rod according to the present invention gets in contact with the moisture in rectum, the rod shaped patch, the tampon, or the rod starts to elute NO on the area to be treated.

In another embodiment these nano-particles, or micro-spheres, may be integrated in a soluble film that disintegrates on the outside of the condom/sheath, condom shaped patch (20, Fig. 2) or rod according to embodiments

of the present invention, in order to elute NO at the area of interest when the soluble film gets in contact with the moisture in rectum, on the area to be treated.

When the NO-eluting device, according to the embodiments of the present invention, gets in contact with the moisture in rectum, said device starts to release NO to the area to be treated. This device does not develop resistance against nitric oxide (NO), is easy to apply, provides a painless treatment, has fast inset of treatment effect, and exclude the necessity of surgery target.

When placed on an area to be treated the device provides prevention and treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, or levator spasm.

In yet another embodiment of the present invention the NO-eluting device is acting as a booster for drug eluting patches, e.g. pharmaceuticals, vitamins, nicotin, nitroglycerin etc. This embodiment presents a device with the advantage of combining two therapeutic treatments, of significant value, in one treatment. Hence, a synergetic effect may be achieved by such devices when NO that is eluted from the device. NO has a vasodilatory effect on the region where the device having the combination compound actuates. Vasodilated tissue is more susceptible to certain medications and thus more easily treated by the medical preparations and still NO has in addition to that the anti-inflamatory, anti-bacterial etc. effect. Hence, an unexpected surprisingly effective treatment is provided.

In another embodiment of the device the fibres, nano-particles, or micro-spheres may be integrated in a gel, cream, or foam that may either be in a smearing or compressed structure. The elution of NO may then be initiated by inserting said gel in rectum. The fibres, nano-particles, or micro-spheres may also be integrated in a hydrogel, which is mixed directly before use. This embodiment has the advantage of being able to penetrate

pockets and corners in rectum, or in the anal area, for closer elution of NO on the area to be treated. A gel, foam, ointment etc. may also be combined with the above mentioned drug boosting effect.

In still another embodiment the nitric oxide eluting polymer, such as powder, nano-particles or micro-spheres, can be incorporated in foam. The foam may have an open cell structure, which facilitates the transport of the proton donor to the nitric oxide eluting polymer. The foam can be of any suitable polymer such as polyurethane, polystyrene, polyester, polyvinylchloride, polyolefins, or latex.

In another embodiment the device is in form of a cream, a gel or a combination of the two. Since the nitric oxide eluting polymer is activated by proton donors the nitric oxide eluting polymer has to be separate from the proton donor until one wants to initiate the elution of nitric oxide, i.e. use the device. One way to accomplish this is to have a syringe with two separate containers. In one container you have a proton donor-based gel and in the other a non proton donor-based gel, comprising the nitric oxide eluting polymer. Upon using the device the two gels are squeezed from the syringe and mixed together, the proton donor in the first gel comes in contact with the nitric oxide eluting polymer in the second gel and the elution of nitric oxide starts.

The device elutes nitric oxide (NO) from said eluting polymer in a therapeutic dose, such as between 0.001 to 5000 ppm, such as 0.01 to 3000 ppm, such as 0.1 to 1000 ppm, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 ppm. The

concentration may vary widely depending on where the concentration is measured. If the concentration is measured close to the actual NO eluting polymer the concentration may be as high as thousands of ppm, while the concentration inside the tissue in this case often is considerably lower, such as between 1 to 1000 ppm.

The devices according to the embodiments of the present invention may be in any suitable diameter sizes, such as a suitable diameter size for inserting said device in rectum, according to above. These devices may also vary in length, which length may be in the interval of 1 to 20 cm, such as 5 to 15 cm, for example 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 cm.

The NO-eluting polymers in the devices according to the present invention may be combined with silver, such as hydroactivated silver. The integration of silver in the devices according to the present invention gives the healing process an extra boost. Preferably the silver is releasable from the devices in the form of silver ions. The integration of silver in the device may present several advantages. One example of such an advantage is that the silver may keep the device in itself free from bacteria or viruses, while the nitric oxide eluting polymer elutes the therapeutic dosage of nitric oxide to the target site.

In the embodiments of the present invention it may be suitable to control or regulate the time span of NO release from the device according to the invention. This may be accomplished by integrating other polymers or materials in said device. These polymers or materials may be chosen from any suitable material or polymer, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl

Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

Three important factors in controlling and regulating the elution of nitric oxide from a nitric oxide eluting polymer are how quickly a proton donor comes in contact with the nitric oxide releasing polymer, such as a diazoliumdiolate group, the acidity of the environment surrounding the nitric oxide eluting polymer, and the temperature of the environment surrounding the nitric oxide releasing polymer (higher temperature promotes elution of nitric oxide).

In one embodiment of the present invention a nitric oxide eluting polymer, such as L-PEI-NO, is mixed with a carrier polymer to slow down or prolong the elution of nitric oxide. Also, in another embodiment, the nitric oxide eluting polymer may be mixed with more than one carrier polymer, whereby be elution or release may be tailor made to fit specific needs. Such a need may for example be a low elution during a first period of time, when the environment of the nitric oxide eluting polymer is hydrophobic, and a faster elution during a second period of time, when the environment of the nitric oxide eluting polymer has been altered to be more hydrophilic. This may for example be accomplished by using biodegradable polymers, whereby a low elution during a first period of time is obtained, after which, when the hydrophobic polymer has been dissolved, the hydrophilic polymer provides a higher elution of nitric oxide. Thus, a more hydrophobic carrier polymer will give a slower elution of nitric oxide, since the activating proton donor, such as water or body fluid, will penetrate the carrier polymer slower. On the other hand, a hydrophilic polymer acts the opposite way. One example of an hydrophilic polymer is polyethylene oxide, and one example of an hydrophobic polymer is polystyrene. These carrier

polymers may be mixed with the nitric oxide eluting polymer and then electrospun to suitable fibers. The skilled person in the art knows which other polymers may be used for similar purposes. Fig. 5 illustrates two elution profiles (NO concentration vs. time) for two different polymer mixtures; a nitric oxide eluting polymer mixed with a hydrophilic carrier polymer in an acidic environment (A), and a nitric oxide eluting polymer mixed with a hydrophobic carrier polymer in a neutral environment (B).

In one embodiment this carrier polymer is substituted by another material with hydrophobic or hydrophilic properties. Therefore, the term "carrier material" in the present context should be interpreted to include carrier polymers and other materials with hydrophilic or hydrophobic properties.

In another embodiment of the present invention the elution of nitric oxide from a nitric oxide eluting polymer, such as L-PEI-NO, is influenced by the presence of protons. This means that a more acidic environment provides a quicker elution of nitric oxide. By activating the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, with an acidic fluid, such as an ascorbic acid solution, the elution of nitric oxide may be accelerated.

The carrier polymers and carrier materials mentioned above may affect other characteristics than the regulation of nitric oxide elution. An examples of such characteristic is mechanical strength.

In respect of the carrier polymers or carrier materials, the NO-eluting polymer may be integrated in, spun together with, or spun on top of, any of these materials in all of the embodiments of the present invention. This spinning includes electro spinning, air spinning, dry spinning, wet spinning, melt spinning, and gel spinning. In this way, one may manufacture fibers of a

polymer mixture, comprising a nitric oxide eluting polymer and a carrier polymer, or a carrier material, with predefined nitric oxide eluting characteristics. These characteristics may be tailor made for different elution profiles in different applications.

The basic material of the device may be polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. The NO-eluting polymer may be integrated in, spun together with, or spun on top of, any of these materials in all of the embodiments of the present invention.

The nitric oxide eluting polymer may comprise a secondary amine, either in the backbone or as a pendant, as described previously. This will make a good nitric oxide eluting polymer. The secondary amine should have a strong negative charge to be easy to load with nitric oxide. If there is a ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, with higher electronegativity than nitrogen (N), it is very difficult to load the polymer with nitric oxide. On the other hand, if there is a electropositive ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, the electronegativity of the amine will increase and thereby increase the possibility to load the nitric oxide elution polymer with nitric oxide.

In an embodiment of the present invention the nitric oxide polymer may be stabilized with a salt. Since the nitric oxide eluting group, such as a diazeniumdiolate

group, usually is negative, a positive counter ion, such as a cation, may be used to stabilize the nitric oxide eluting group. This cation may for example be selected from the group comprising any cation from group 1 or group 2 in the periodic table, such as Na^+, K^+, Li^+, Be^{2+}, Ca^{2+}, Mg^{2+}, Ba^{2+}, and/or Sr^{2+}. Different salts of the same nitric oxide eluting polymer have different properties. In this way a suitable salt (or cation) may be selected for different purposes. Examples of cationic stabilized polymers are L-PEI-NO-Na, i.e. L-PEI diazeniumdiolate stabilized with sodium, and L-PEI-NO-Ca, i.e. L-PEI diazeniumdiolate stabilized with calcium.

Another embodiment of the present invention comprises mixing the nitric oxide eluting polymer, or a mixture of the nitric oxide eluting polymer and a carrier material, with an absorbent agent. This embodiment provides the advantage of an accelerated elution of nitric oxide since the polymer, or polymer mixture, via the absorbent agent, may take up the activating fluid, such as water or body fluid, much faster. In one example 80 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, and in another embodiment 10 to 50 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material.

Since the elution of nitric oxide is activated by a proton donor, such as water, it may be an advantage to keep the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, in contact with said proton donor. If an indication requires an elution of nitric oxide during a prolonged period of time, a system is advantageous, which presents the possibility to keep the proton donor in contact with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and

carrier material. Therefore, in still another embodiment of the present invention, the elution of nitric oxide may be regulated by adding an absorbent agent. The absorbent agent absorbs the proton donor, such as water, and keeps the proton donor in close contact with the nitric oxide eluting polymer during prolonged periods of time. Said absorbent agent may be selected from the group comprising polyacrylates, polyethylene oxide, carboxymethylcellulose, and microcrystalline cellulose, cotton, and starch. This absorbent agent may also be used as a filling agent. In this case said filling agent may give the nitric oxide eluting polymer, or mixture of said nitric oxide eluting polymer and a carrier material, a desired texture.

The device may be manufactured by, for example electro spinning of L-PEI. L-PEI is the charged at a characteristic voltage, and a fine jet of L-PEI releases as a bundle of L-PEI polymer fibres. This jet of polymer fibres may be directed to a surface to be treated. The surface to be treated may for example be any suitable material in respect of a device. The electro spun fibres of L-PEI then attach on said material and form a coating/layer of L-PEI on the certain embodiments of the device according to the invention. L-PEI may also be combined with other polymers comprising L-PEI or being arranged in combination with L-PEI.

It is of course possible to electro spin the other NO-eluting polymers, according to above, on the device according to the invention while still being inside the scope of the present invention.

In one embodiment the NO-eluting polymers according to the present invention are electro spun in such way that pure NO-eluting polymer fibres may be obtained.

Gas stream spinning, air spinning, wet spinning, dry spinning, melt spinning, or gel spinning, of said NO-

eluting polymers onto the device is also within the scope of the present invention.

The manufacturing process according to the present invention presents the advantages of large contact surface of the NO-eluting polymer fibres with the area to be treated, effective use of NO-eluting polymer, and a cost effective way of producing the device.

Hereinafter, some potential uses of the present invention are described:

A method of therapeutical treatment of rectal disorders, including fissures, ulcers, haemorrhoids, and levator spasm by means of a device comprises a nitric oxide (NO) eluting polymer configured for eluting a therapeutic dosage of nitrogen oxide (NO) when used for said treatment, comprising exposing a rectal treatment site of said rectal disorder in or on a rectal region of a body to said nitric oxide when said polymer in use elutes nitrogen oxide (NO) by eluting a therapeutic dose of nitric oxide from said nitric oxide eluting polymer to said treatment site.

The method according to the above, wherein said rectal treatment site of said rectal disorder is a rectum, and wherein said method comprises applying a condom/sheath, a rod shaped pad, rod, and/or a tampon to said rectum for said exposure.

Use of nitric oxide (NO) in a therapeutic dose for therapeutically treating rectal fissures, ulcers, haemorrhoids, and/or levator spasm.

The invention may be implemented in any suitable form. The elements and components of the embodiments according to the invention may be physically, functionally, and logically implemented in any suitable way. Indeed, the functionality may be implemented in a single unit, in a plurality of units, or as part of other functional units.

Although the present invention has been described above with reference to specific embodiments, it is not

intended to be limited to the specific form set forth herein. Rather, the invention is limited only by the accompanying claims and, other embodiments than the specific above are equally possible within the scope of these appended claims.

In the claims, the term "comprises/comprising" does not exclude the presence of other elements or steps. Furthermore, although individually listed, a plurality of means, elements or method steps may be implemented. Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms "a", "an", "first", "second" etc do not preclude a plurality. Reference signs in the claims are provided merely as a clarifying example and shall not be construed as limiting the scope of the claims in any way.

CLAIMS

1. A device configured to therapeutically treat or prevent rectal disorders, including fissures, ulcers, haemorrhoids, and levator spasm, wherein

said device comprises a nitric oxide (NO) eluting polymer configured to elute a therapeutic dosage of nitrogen oxide (NO) when used for said treatment and/or prevention, and

wherein said device is configured to expose a rectal treatment site of said rectal disorder in or on a rectal region of a body to said nitric oxide when said polymer, in use, elutes nitrogen oxide (NO),

c h a r a c t e r i z e d in that

said nitric oxide (NO) eluting polymer is integrated with a carrier material, such that said carrier material, in use, regulates and controls the elution of said therapeutic dosage of nitric oxide (NO).

2. Device according to claim 1, wherein said nitric oxide (NO) eluting polymer comprises diazeniumdiolate groups, S-nitrosylated groups, and O-nitrosylated groups, or any combination these.

3. Device according to claim 1 or 2, wherein said nitric oxide (NO) eluting polymer is L-PEI (linear polyethyleneimine), loaded with nitric oxide (NO) through said diazeniumdiolate groups, S-nitrosylated groups, or O-nitrosylated groups, or any combination these, arranged to release nitric oxide (NO) at said rectal treatment site of said rectal disorder.

4. Device according to claim 1, wherein said nitric oxide eluting polymer is selected from the group comprising amino cellulose, amino dextrans, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose,

polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

5. Device according to claim 1, in a form selected from the group comprising of a condom/sheath, a rod shaped pad, rod, and a tampon, adapted to be applied on or at said rectal treatment site .

6. Device according to claim 5, wherein said condom/sheath, condom shaped pad, rod, or tampon is manufactured of polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these, and said condom/sheath, condom shaped pad, rod, or tampon, includes said nitric oxide (NO) eluting polymer configured to, in use, elute said nitric oxide (NO) to said rectal treatment site said treatment thereof.

7. Device according to claim 1, wherein said device is partly disintegrable when subjected to moisture or water.

8. Device according to claim 1, wherein said polymer comprises silver, configured for therapeutic treatment of said rectal treatment site of said rectal disorder.

9. Device according to claim 1, configured to act as a booster for drugs or pharmaceutical compounds.

10. Device according to claim 1, wherein said polymer is comprised in said device in form of nano-particles or micro-spheres.

11. Device according to claim 10, wherein said nano-particles or micro-spheres are integrated in a gel, hydrogel, foam or cream.

12. Device according to claim 10, wherein said nano-particles, or micro-spheres, are encapsulated in a material, selected from the group consisting of polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

13. Device according to claim 1, wherein said carrier material, which regulates and/or controls NO-elution, is selected from the group comprising polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

14. Device according to claim 1, wherein said NO-eluting polymer is applied on, or integrated with, a material selected from the group comprising polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

15. Device according to claim 1, wherein said nitric oxide eluting polymer comprises a secondary amine in the backbone or a secondary amine as a pendant.

16. Device according to claim 15, wherein a positive ligand is located on a neighbour carbon atom to the secondary amine.

17. Device according to claim 1 or 13, comprising an absorbent agent.

18. Device according to claim 17, wherein said absorbent agent is selected from the group comprising polyacrylate, polyethylene oxide, Carboxy Methyl Cellulose (CMC), microcrystalline cellulose, cotton, or starch, or any combinations thereof.

19. Device according to claim 1, 13, 14, 15, 16, or 17, comprising a cation, said cation stabilizing the nitric oxide eluting polymer.

20. Device according to claim 19, wherein said cation is selected from the group comprising Na^+, K^+, Li^+, Be^{2+}, Ca^{2+}, Mg^{2+}, Ba^{2+}, and/or Sr^{2+}, or any combinations thereof.

21. A device according to any of the preceding claims, wherein said nitric oxide (NO) eluting polymer is activateable to elute said therapeutic dosage of nitrogen oxide (NO) by water.

22. Device according to claim 1, wherein said carrier material is a hydrogel.

23. Device according to claim 1, wherein the nitric oxide eluting polymer is activateable by proton donors, wherein a the nitric oxide eluting polymer is, prior to use, stored separate from the proton donor until initiation of elution of nitric oxide therefrom.

24. Device according to claim 23, wherein the device is a syringe-type device having two separate containers, wherein a first container contains a proton donor-based NO release activation agent, such as a gel, and a second container contains a non proton donor-based gel, comprising the nitric oxide eluting polymer, wherein the syringe-type device is configured to provide admixing upon administration to said rectal region.

25. A manufacturing process for a device configured to therapeutically treat or prevent rectal disorders, including fissures, ulcers, haemorrhoids, and levator spasm, at a rectal region of a body, according to claim 1, comprising:

selecting a nitric oxide (NO) eluting polymer configured to elute a therapeutic dosage of nitric oxide (NO) when used for said therapeutic treatment and/or prevention of rectal disorders,

selecting a carrier material, which carrier material is configured to regulate and control the elution of said therapeutic dosage of nitric oxide (NO),

incorporating the NO-eluting polymer with said carrier material into an nitric oxide (NO) eluting material, such that said carrier material, in use of said device, regulates and controls the elution of said therapeutic dosage of nitric oxide (NO), and

deploying said nitric oxide eluting material into a suitable form, or as a coating onto a carrier, to form at least a part of said device, such that said device is configured to expose a rectal region to said nitric oxide when said NO-eluting polymer in use elutes nitric oxide (NO).

26. The manufacturing process according to claim 25,

wherein said deploying comprises electro spinning, air spinning, gas spinning, wet spinning, dry spinning, melt spinning, or gel spinning of NO-eluting polymer.

27. The manufacturing process according to claim 25 or 26, wherein said selecting said nitric oxide (NO) eluting polymer comprises selecting a plurality of nitric oxide (NO) eluting polymeric particles, preferably nano fibres, nano particles or micro spheres.

28. The manufacturing process according to claim 25 or 26, wherein said incorporating said NO-eluting polymer with said carrier material comprises integrating said NO-eluting polymer in said carrier material, spinning said NO-eluting polymer together with said carrier material, or spinning said NO-eluting polymer on top of said carrier material, in order to predefine nitric oxide eluting characteristics of said device.

29. The manufacturing process according to claim 25, further comprising integrating silver in said device.

30. The manufacturing process according to claim 25, further comprising microencapsulating proton donor in micro capsules, and

applying the micro capsules to said nitric oxide (NO) eluting material.

31. The manufacturing process according to claim 30, wherein said applying comprises pattern gluing, or spinning the NO eluting material onto said micro capsules.

32. Use of a nitric oxide (NO) eluting polymer for the manufacture of a device for the treatment of rectal disorders, including fissures, ulcers, haemorrhoids, and levator spasm wherein

said nitric oxide is loaded to said device elutes nitric oxide (NO) from said eluting polymer in a therapeutic dose when used at a site of treatment in or on a body.

33. Use according to claim 32, wherein said therapeutic dose is 0.001 to 5000 ppm, such as 0.01 to 3000 ppm, such as 0.1 to 1000 ppm, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 ppm.

34. Use of nitric oxide (NO) in a therapeutic dose for therapeutically treating and/or preventing levator spasm at a treatment side of a body.

35. Use of nitric oxide (NO) in a medicament for therapeutically treating and/or preventing levator spasm at a treatment side of a body.

36. Use of nitric oxide (NO) in a therapeutic dose for therapeutically treating and/or preventing haemorrhoids at a treatment side of a body.

37. Use of nitric oxide (NO) in a medicament for therapeutically treating and/or preventing haemorrhoids at a treatment side of a body.

38. Use of nitric oxide (NO) in a therapeutic dose for therapeutically treating and/or preventing fissures at a treatment side of a body.

39. Use of nitric oxide (NO) in a medicament for therapeutically treating and/or preventing fissures at a treatment side of a body.

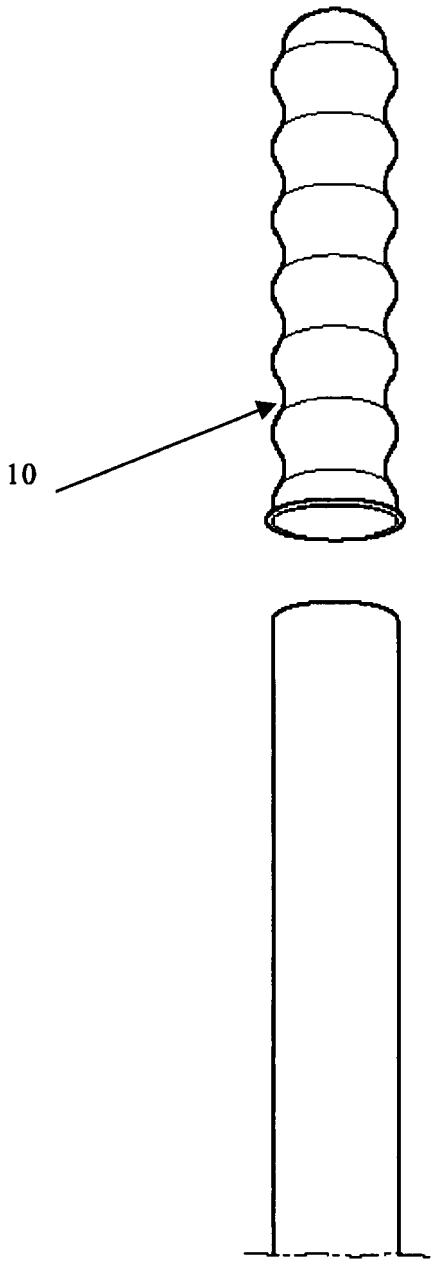

Fig. 1

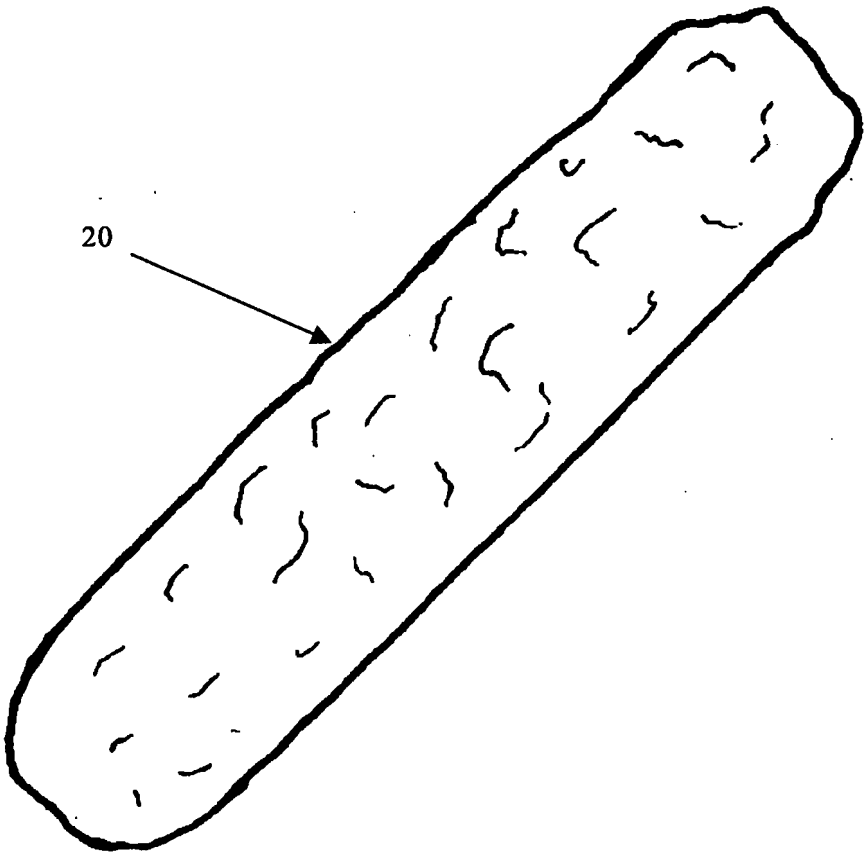

Fig. 2

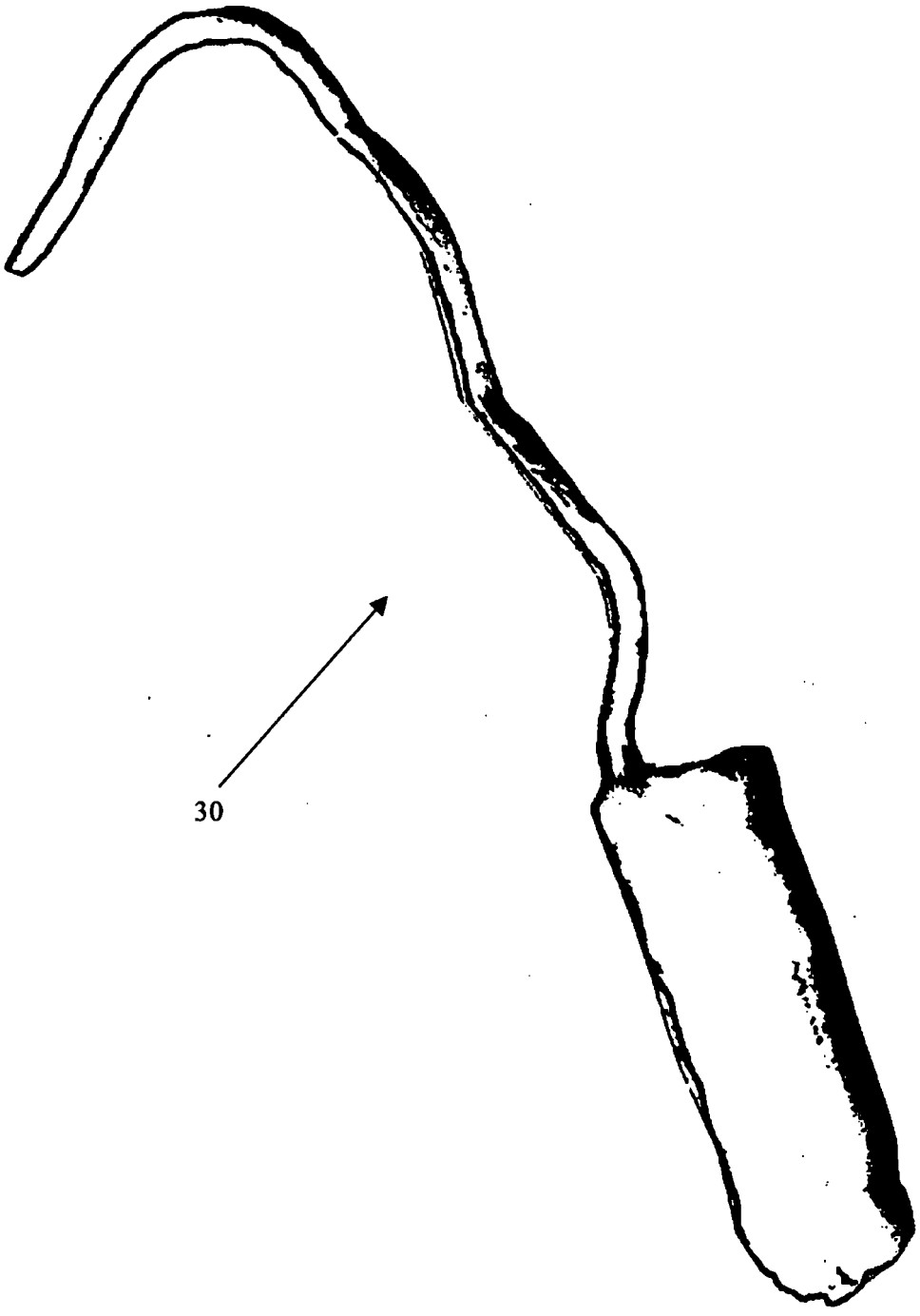

Fig. 3

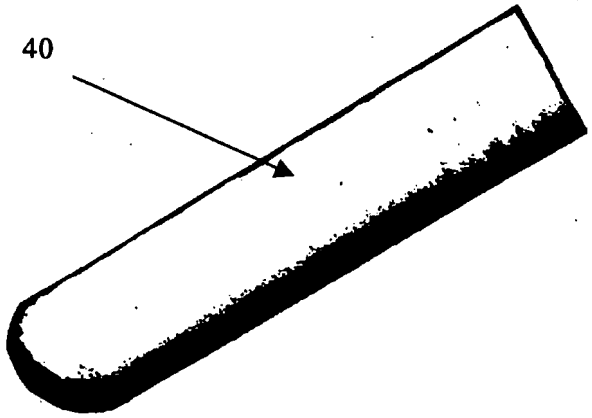
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Fig. 4

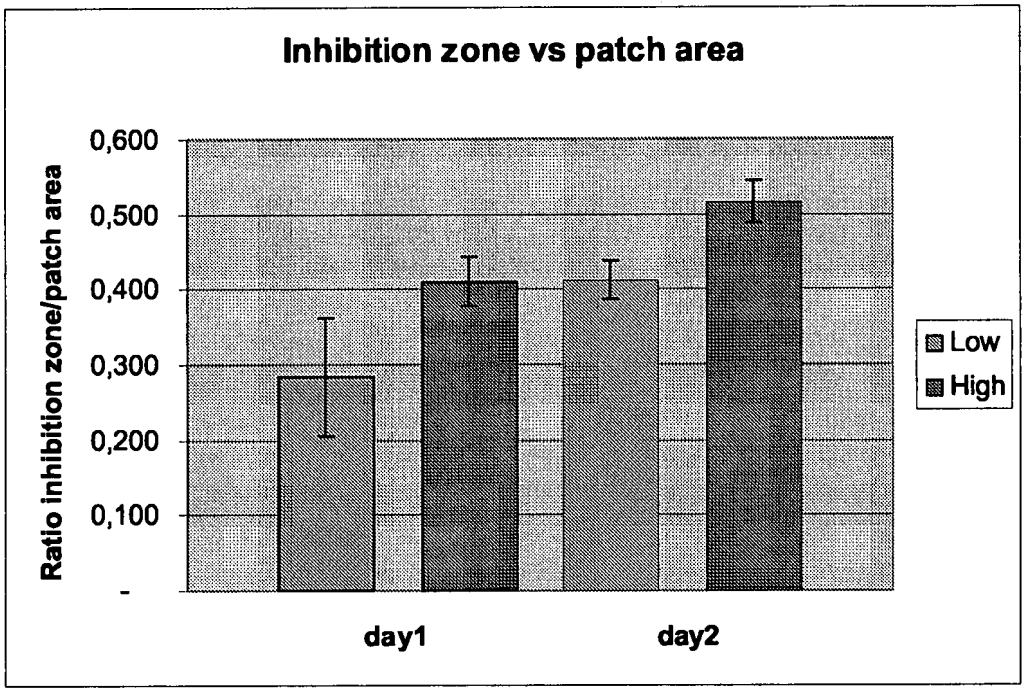
Inhibition zone vs patch area
Ratio inhibition zone/patch area
0,600
0,500
0,400
0,300
0,200
0,100
-
day1
day2
Low
High

Fig. 5

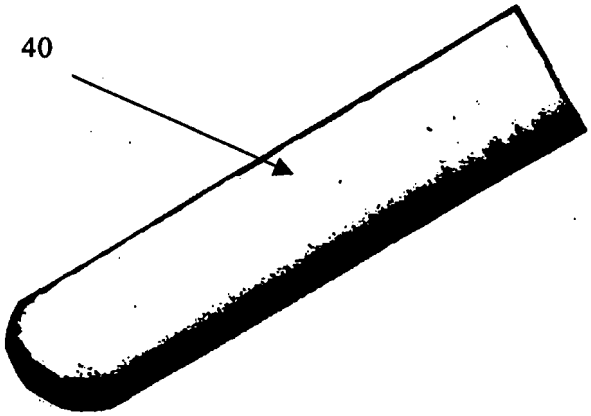
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Fig. 4

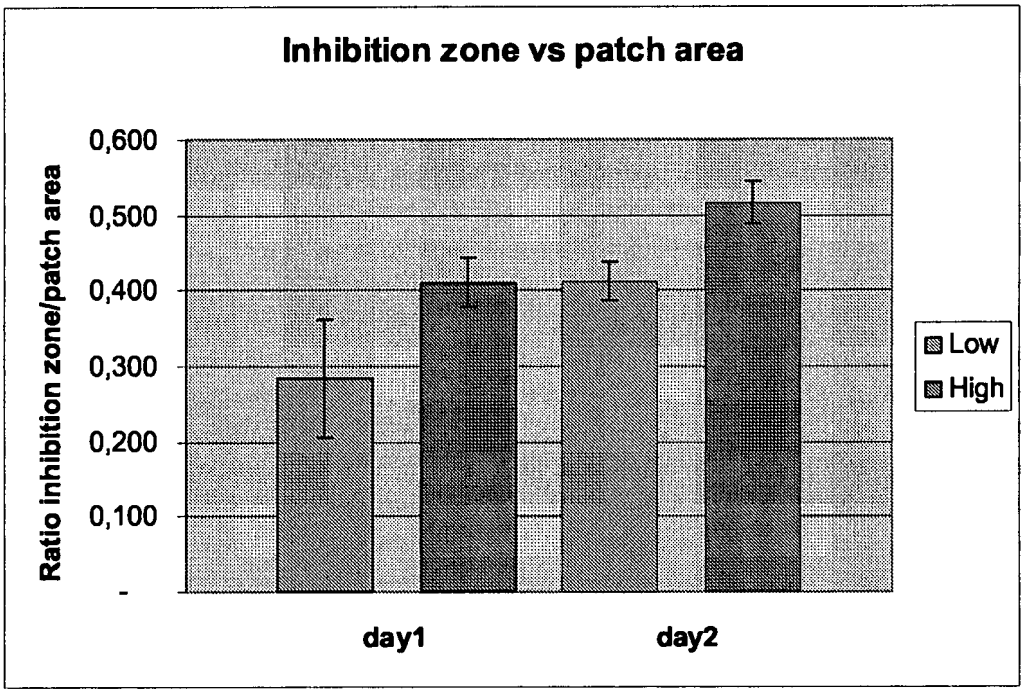
Inhibition zone vs patch area
Ratio inhibition zone/patch area
0,600
0,500
0,400
0,300
0,200
0,100
-
day1
day2
Low
High

Fig. 5